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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/603,891	BUECHLER ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 37, and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn as claims 37 and 38 were inadvertently not included in the Final Rejection dated October 31, 2007.

2. In view of the above reopening of the prosecution, the Pre-Appeal Conference request dated February 29, 2008 have been put on hold in order to address patentability of claims 37 and 38 under 37 CFR 1.104.

3. Applicants' reply filed on February 29, 2008 have been acknowledged and entered. The reply does not include any claim amendments.

4. Claims 1-17, 37, and 38 are pending and under consideration for patentability under 37 CFR 1.104.

5. As a preliminary matter, the dependency of claim 38 has been interpreted as being dependent on claim 37 rather than being self-dependent for the examination purpose (see below rejection of claim 38 under 35 U.S.C. 112, second paragraph). Further, claim 37 currently recites combination of cardiovascular disorders, which are

directed to non-elected species of cardiovascular disorder, as the species of pulmonary embolism was elected as the cardiovascular disorder in the reply filed on July 6, 2006. Since claim 38 recites a combination of cardiovascular disorders, which includes the elected cardiovascular disorder of pulmonary embolism and encompasses the combination of cardiovascular disorders recited in claim 37, the combination of cardiovascular disorders recited claim 37 has been considered to further include pulmonary embolism for the purpose of examination.

Claim Objections

6. Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim (claim 37). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 37 recites a step of "characterizing said subject's risk of having developed or of developing one or more myocardial infarction and congestive hear failure based upon the presence or amount of the markers assayed in step (a)." This step of claim 37 includes a Markush alternative disorders selected from myocardial infarction and congestive hear failure. Further inclusion of pulmonary embolism as recited in claim 38 broadens the scope of the dependent claim 38. Therefore, claim 38 fails to further limit the subject matter of previous claim 37.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is vague and indefinite as claim 38 is dependent on itself. For the purpose of examination, claim 38 has been interpreted as being dependent on claim 37.

Claim Rejections - 35 USC § 112, first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Written Description

Claims 1-10, 13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP states that the purpose of the written description requirement is to ensure that the inventor ad possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

> "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice...or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" MPEP § 2163.

The MPEP does state that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosures of two chemical compounds

within a subgenus did not describe that subgenus. In re Gostelli 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of analyzing a subject sample for a plurality of subject-derived marker selected to distinguish amongst a plurality of cardiovascular disorders, wherein the subject-derived markers include at least one blood pressure regulation markers and at least one myocardial injury markers.

The claims are not limited as to the number of markers, since claim 1 recites "one or more subject-derived markers" and would encompass, for example 20 different blood regulation markers, 18 myocardial injury markers, 18 inflammation markers, and 15 coagulation and hemostasis markers as recited in claims 3, 7, and 11. The specification discloses that these markers can be combined into panels comprising 1-20 or more markers (p101, paragraph [0241]), which means that there are at least more than $2x10^{61}$ different panels that can be made up from various possible marker combinations, i.e. $2x10^{61}$ different assays measuring different sets of markers in order to carry out the claimed invention. The prior art does not teach methods of determining all possible panels to distinguish amongst a plurality of cardiovascular disorders (since presumably not all of the markers would be indicative of all cardiovascular disorders). However, the specification provides data for fewer than 9 different marker combinations for distinguishing a plurality of cardiovascular disorders, which only include myocardial infarction (MI), congestive heart failure (CHF), acute coronary syndrome, unstable angina, and pulmonary embolism (p7, paragraph [0022], p9, paragraph [0028], and Examples 3-5). Therefore, the specification would not reasonably convey possession of

the entire genus of the more than $2x10^{61}$ different marker panels encompassed by the claims.

Instant claims recite a genus "subject-derived markers" related to blood pressure regulation, myocardial injury, inflammation, and coagulation and hemostasis as part of the invention without providing a physical structure or testable functional activity for the "subject-derived markers."

BNP is associated with raised atrial and pulmonary wedge pressures, reduced ventricular systolic and diastolic function, left ventricular hypertrophy, MI, CHF, and renal failure (pp31-32). ANP is associated with hypervolemia, atrial fibrillation, and CHF (pp34-36). Therefore, while the above subject-derived markers can be used for can be used for determining the absence of certain cardiovascular disorders, the above subject-derived markers cannot be used for characterizing the risk of having developed or developing a specific cardiovascular disorder as currently recited in the claims since plurality of disease conditions can be responsible for the elevated levels of ANP and BNP.

C-type natriuretic peptide (CNP) is associated with blood pressure regulation (p93) and cerebral injuries (p38, paragraph [0130]). The specification does not disclose any cardiovascular disorders relating to urotensin II (p89, paragraph [0213]), arginine (p93), aldosterone (p93), angiotensin I (p94), angiotensin II (pp90-91), angiotensin III (p94), bradykinin (p94), calcitonin (p90), calcitonin gene related peptide (p90), adrenomedullin (pp88-89), calcyphosine (p95), endothelin-2 (p89), endothelin-3 (p89), renin (p94), and urodilatin (p94). Vasopressin is associated with heart failure (pp89-90).

Procalcitonin is associated with sepsis (pp72-73). Therefore, the current specification fails to describe how these subject-derived markers can be used to characterize a subject's risk of having developed or developing plurality of cardiovascular disorders.

With respect to the markers related to inflammation as recited in claims, the specification discloses the following markers related to inflammation and their association with variety of disease conditions. C-reactive protein (CRP) is associated with acute MI, unstable angina, infection, surgery, trauma, stroke, atherosclerotic plaque rupture, and cardiac tissue injury (pp64-65). Interleukins (IL-1 and IL-6) are associated with trauma, infection, acute MI, and unstable angina (pp66-68) and IL-1 receptor agonists are associated with acute MI, death, refractory angina, infection, trauma, and arthritis (p66-67). CD54 (soluble intercellular adhesion molecule, sICAM-1) is associated with acute MI, unstable angina, atherosclerosis, atherosclerotic plaque rupture, ischemic stroke, head trauma, cancer, preeclampsia, multiple sclerosis, cystic fibrosis, and other nonspecific inflammatory states (p69). CD106 (vascular cell adhesion molecule, VCAM) is associated with acute MI, unstable angina, stable angina, atherosclerosis, ischemic strok, cancer diabetes, preeclampsia, vascular injury, and other nonspecific inflammatory states (p70). Monocyte chemotactic protein-1 (MCP-1)is associated with pathogenesis of variety of disease including psoriasis, rheumatoid arthritis, atherosclerosis, acute MI, unstable angina, alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus (pp70-71). Caspase-3 is associated with ischemia and hypoxia (pp91-92). Human lipocalin-type prostaglandin D synthase (hPDGS) is associated with unstable angina, cerebral infarction (p71). Mast

cell tryptase is associated with allergic airway inflammation and variety of allergic conditions (p72). Eosinophil cationic protein (ECP) is associated with asthma and pulmonary inflammation in bronchial asthma (p72). KL-6 is associated with lung diseases such as pulmonary fibrosis, interstitial pneumonia, sarcoidosis, and interstitial pneumonitis (p72). Haptoglobin is associated with inflammation (p93). Tumor necrosis factor α is associated with acute MI, unstable angina, trauma, stroke, and infection (pp68-69). Tumor necrosis factor β (p97), fibronectin (p95), and vascular endothelial growth factor (VEGF, p86) are not disclosed in the specification to be associated with any cardiovascular disease conditions. Therefore, while some of the inflammatory related subject-derived markers can be used for can be used for determining the absence of cardiovascular disorders, these inflammatory related subject-derived markers cannot be used for characterizing the risk of having developed or developing a specific cardiovascular disorder as currently recited in the claims since plurality of disease conditions can be responsible for the assayed subject-derived markers. Further, the current specification fails to describe how some of the above inflammatory related subject-derived markers can be used to characterize a subject's risk of having developed or developing plurality of cardiovascular disorders.

With respect to the markers related to coagulation and hemostasis as recited in claims, the specification discloses the following markers related to coagulation and hemostasis and their association with variety of disease conditions. D-dimer is associated with any condition associated with coagulation and fibrinolysis activation and can be used to exclude pulmonary embolism (p32). Plasmin is associated with

atherosclerosis, disseminated intravascular coagulation, acute MI, surgery, trauma, unstable angina, stroke, and thrombotic thrombocytopenic purpura (p45). β-Thromboglobulin is associated with atherosclerosis, disseminated intravascular coagulation, surgery, trauma, stroke, and thrombotic thrombocytopenic purpura (p46). PF 4 is associated with atherosclerosis, disseminated intravascular coagulation, acute MI, surgery, trauma, unstable angina, acute stroke, and thrombotic thrombocytopenic purpura (pp46-47). FPA is associated with stroke, surgery cancer, disseminated intravascular coagulation, nephrosis, and thrombotic thrombocytopenic purpura (p47). PDGF is associated with pro-inflammatory conditions, surgery trauma, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and vascular injury (p48). Prothrombin fragment 1+2 is associated with stroke, surgery, trauma, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation (pp48-49). P-selectin is associated with acute MI, unstable angina, exercise stress test, idiopathic thrombocytopenic purpura, rheumatoid arthritis, hypercholesterolemia, acute stroke, atherosclerosis, hypertension, acute lung injury, connective tissue disease, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, and chronic renal failure (pp49-51). Thrombin is associated with acute MI, unstable angina, stroke, surgery, trauma, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura (pp51-52). vWF is associated with stroke, acute MI, unstable angina, subarachnoid hemorrhage (pp52-54). Tissue factor is associated with ischemic hear disease, acute MI, angina, atherosclerotic plaques, subarachnoid hemorrhage, disseminated intravascular coagulation, renal failure, vasculitis, and sickle

cell disease (pp54-56). Other than D-dimer, subject-derived markers such as plasmin, β-thromboglobulin, PF4, FPA, PDGF, prothrombin fragment 1+2, P-selectin, thrombin, vWF, and tissue factor are not disclosed in the specification as being associated with pulmonary embolism and therefore cannot be used to characterize the risk of having developed or developing pulmonary embolism. Further, these inflammatory related subject-derived markers cannot be used for characterizing the risk of having developed or developing a specific cardiovascular disorder as currently recited in the claims since plurality of disease conditions can be responsible for the assayed subject-derived markers. Further, the current specification fails to describe how some of the above coagulation and hemostasis related subject-derived markers can be used to characterize a subject's risk of having developed or developing a cardiovascular disorder since plurality of disease conditions can be responsible for the assayed subject-derived markers.

Since each marker represents a unique polypeptide of distinct structure and functional properties, methods that involve the detection of different markers or different sets of markers would differ substantially. For example, any given marker would not be capable of distinguishing "all cardiovascular disorders." In light of substantial variance among the genus of methods claimed, one skilled in the art would not understand the inventor(s) to have possession of the entire genus based on the limited methods described.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of claims and does not reasonably convey to one skilled in the

relevant art that the inventor(s), at the time of the application was filed, had possession of the entire genus of the claimed invention.

11. Enablement

Claims 1-10, 13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for distinguishing between MI, congestive heart failure (CHF), and pulmonary embolism using subject-derived markers comprising cardiac-specific troponin isoforms, B-type natriuretic peptide (BNP), and D-dimer (see p7, paragraph [0022] of the specification), does not reasonably provide enablement for a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders, wherein the subject-derived markers include blood pressure regulation, myocardial injury, inflammation, coagulation and hemostasis related markers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is drawn to a method of analyzing a subject sample for a plurality of subject-derived markers selected to distinguish amongst a plurality of cardiovascular disorders, wherein the subject-derived markers include at least one blood pressure regulation markers and at least one myocardial injury markers. The invention is further drawn to assaying for additional subject-derived markers related to inflammation and coagulation and hemostasis.

The claims are broad in many aspects. Distinguishing amongst a plurality of cardiovascular disorders is not limited, and therefore the plurality of cardiovascular disorders can include any abnormalities of the heart and vasculature as defined by the original specification (p18, paragraph [0057]). The term "cardiovascular disorders" is intended to include, but is not limited to, renovascular hypertension, CHF, aortic aneurysm, iliac or femoral aneurysm, pulmonary embolism, MI, acute coronary syndrome, angina, primary hypertension, atrial fibrillation, systolic dysfunction, diastolic dysfunction, myocarditis, atherosclerosis, atrial tachycardia, ventricular fibrillation, endocarditis, and peripheral vascular disease (p18, paragraph [0057]). Thus, the term "cardiovascular disorders" include list provided in the original specification as discussed above as well as cardiovascular disorders, which have not been specifically disclosed by the specification. With regards to the distinguishing amongst a plurality of cardiovascular disorders, the number of subject-derived markers needed in a panel to distinguish amongst a plurality of cardiovascular disorders is governed by the number of the plurality of cardiovascular disorders. The specification defines the term "plurality" as being "at least two" and "at least 100" in particularly preferred embodiments (p21, paragraph [0070]). As the number of types of cardiovascular disorders increases, the number of subject-derived markers needed in a panel would increase as many of the markers disclosed in the specification as well as the elected species of markers (discussed below) are associated with one or more cardiovascular disorders. In addition, the claims are directed to using a plurality of subject-derived markers, in which the subject-derived markers include at least one blood pressure regulation markers and

at least one myocardial injury markers in order to distinguish amongst a plurality of cardiovascular disorders. Additional subject-derived markers related to inflammation and coagulation and hemostasis are further included. In addition to the list of specific type of the markers recited in claims 3, 7, and 11, the terms "subject-derived markers related to blood pressure regulation", "subject-derived markers related to myocardial injury", "subject-derived markers related to inflammation", and "subject-derived markers related to coagulation and hemostasis" would include other blood pressure regulation, myocardial injury, inflammation, and coagulation and hemostasis related markers, which have not been disclosed in the specification. The claims recite 20 different blood regulation markers, 18 myocardial injury markers, 18 inflammation markers, and 15 coagulation and hemostasis markers. The specification discloses that these markers can be combined into panels comprising 1-20 or more markers (p101, paragraph [0241]), which means that there are at least more than $2x10^{61}$ different panels that can be made up from various possible marker combinations, i.e. $2x10^{61}$ different assays measuring different sets of markers in order to carry out the claimed invention. However, the specification provides data for fewer than 9 different marker combinations for distinguishing a plurality of cardiovascular disorders, which only include MI, congestive, heart failure, acute coronary syndrome, unstable angina, and pulmonary embolism (p7, paragraph [0022], p9, paragraph [0028], and Examples 3-5). The specification fails to teach the skilled artisans how to detect all subject-derived markers in all sample types and how to use this information in distinguishing a cardiovascular

disorder amongst a plurality of cardiovascular disorders (see description of subject-derived markers disclosed in the current specification set forth in item 10 above).

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108, F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1996) (stating, in context of the utility requirement, that a "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id.

In the instant case, such reasonable detail is lacking. The specification lists a large number of different subject-derived markers, and suggests that one skilled in the art would use information relating to the presence or amount of various different combinations of these markers in order to distinguish a cardiovascular disorder amongst a plurality of cardiovascular disorders. However, the specification fails to identify which specific panel of markers should be measured for each type of cardiovascular disorder amongst a specific group of cardiovascular disorders. The specification further fails to disclose what levels of each marker would be indicative of a particular cardiovascular disorder.

Although the specification outlines art-recognized methodology that can be used in conducting investigational studies to test and validate biomarkers for various diagnostic purposes, such a general roadmap amounts to an invitation to conduct further research, rather than a specific direction required to enable one of ordinary skill in the art to understand and carry out the invention. Hence, this general outline for how

to test and validate different sets of biomarkers for distinguishing amongst a plurality of cardiovascular disorders fails to constitute an enabling disclosure in light of complexity, unpredictability and laborious nature of biomarker validation (discussed further below) and furthermore fails to provide one skilled in the art with any reasonable expectation of success in using any particular combination of markers to distinguish amongst a plurality of cardiovascular disorders. The specification sets forth a research plan, not an invention to be practiced.

As a result, in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid biomarkers of the particular cardiovascular disorder, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods. This type of clinical investigations would need to be done for each type of cardiovascular disorder. In addition, one skilled in the art would also need to determine what levels or ranges of levels of each of the markers would be indicative of each type of cardiovascular disorder. Such investigative research to test and validate all of the biomarkers for use in distinguishing a cardiovascular disorder is not of a routine nature and clearly represents an undue burden.

For example, Bast, Jr. et al. (*Clinical Cancer Research*, 2005, Vol. 11, pp6103-6108) point to the "lengthy process" of assay development and validation and note that

many markers that correlate with disease statistically may not prove to be useful clinically (p6105, right column). Similarly, LaBaer et al. (*Journal of Proteome Research*, 2005, Vol. 4, pp1053-1059) teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p1053, paragraph bridging the left and right columns). In addition, Baker (*Nature Biotechnology*, 2005, Vol. 23, pp297-304) speaks to the unpredictability involved in clinically applying biomarkers (p298, *Walking on Thin Ice*).

Regarding the claimed invention as read on elected species of pulmonary embolism, the specification is enabled for assaying a sample for the amount of subject-derived markers comprising BNP, free and complexed troponin T, and D-dimer. Claims 1-10, 13, and 15-17 are drawn to a method of analyzing a subject sample for a plurality of subject-derived markers, which do not include D-dimer. However, the specification does not reasonably provide enablement for using subject-derived markers, which do not include D-dimer. The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). None of the markers related to blood pressure regulation, myocardial injury, and inflammation as

disclosed in the specification and recited claims 3 and 7 can be used specifically to distinguish pulmonary embolism. Furthermore, markers related coagulation and hemostasis as recited in claim 11 with an exception of D-dimer are not specific markers of pulmonary embolism. The summary of each class of markers is disclosed in the specification (pp30-73). For example, Markers related to blood pressure include A-type natriuretic peptide (ANP) and BNP. Elevations of BNP are associated with raised atrial and pulmonary wedge pressures, reduced ventricular systolic and diastolic function, left ventricular hypertrophy, MI, CHF, and renal failure (pp31-32, paragraph [0109]). Elevated levels of ANP are found during hypervolemia, atrial fibrillation, and CHF. discloses number of markers related to blood pressure regulation, myocardial injury, and inflammation and their association with specific disorders. Free and complexed troponin T, a myocardial injury related marker, provide information related to the presence of progressing myocardial damage (p33, paragraph [0115]). Elevations of C-reactive protein (CRP), an inflammation related marker, have been identified in the plasma of individuals with acute MI and unstable angina, most likely a result of activation of acute phase response associated with atherosclerotic plaque rupture or cardiac tissue injury (p65, paragraph [0166]). Elevations in the plasma concentration of platelet factor 4 (PF4), a coagulation and hemostasis related marker, is associated with clot presence, or any condition that causes platelet activation, which include atherosclerosis, disseminated intravascular coagulation, surgery, trauma, thrombotic thrombocytopenic purpura, and acute stroke (pp46-47, paragraph [0144]). Therefore, the markers related to blood pressure regulation, myocardial injury, inflammation, and

coagulation and hemostasis with an exception of D-dimer do not satisfy features of diagnostic markers for pulmonary embolism as these markers are indicators of other cardiovascular disorders as discussed above and are not capable of specifically distinguishing pulmonary embolism amongst other cardiovascular disorders.

With regards to the elected invention of distinguishing pulmonary embolism using elected species of markers comprising BNP, free and complexed troponin T, and C-reactive protein (claims 1-8), the specification discloses that the skilled artisan will recognize that, for example, increased BNP is indicative of CHF, but may also be indicative of other cardiac-related conditions such as MI (p35, paragraph [0121]). Thus, the inclusion of a marker related to myocardial injury such as cardiac troponin I and/or cardiac troponin T could permit further discrimination of the disease underlying the observed dyspnea and the increased BNP level. In this case, an increased level of cardiac troponin may be used to rule in MI (p35, paragraph [0121]). Similarly, BNP may also be indicative of pulmonary embolism (p35, paragraph [0122]). The inclusion of a marker related to coagulation and hemostasis such as D-dimer can permit further discrimination of the disease underlying the observed dyspnea and the increased BNP level (p35, paragraph [0121]). In this case, a normal level of D-dimer may be used to rule out pulmonary embolism (p35, paragraph [0121]). As discussed above, BNP, free and complexed troponin T, and C-reactive protein are not specifically associated with pulmonary embolism. Therefore, D-dimer is used to distinguish pulmonary embolism since BNP, free and complexed troponin T, and C-reactive protein do not specifically distinguish pulmonary embolism amongst cardiovascular disorders.

In summary, the specification lists a large number of possible subject-derived markers and suggests the use of various combinations of the subject-derived markers for distinguishing a cardiovascular disorder amongst a plurality of cardiovascular disorders. However, the specification lacks clinical data validating the various biomarker combinations corresponding to a specific cardiovascular disorder to be distinguished, and fails to disclose specific guidance regarding, which specific panels of markers are to be used to distinguish a cardiovascular disorder amongst how many cardiovascular disorders and what levels would be indicative of a specific cardiovascular disorder. Taken together with the breadth of the claims and the unpredictability associated with validation of biomarkers for clinical use, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without further undue experimentation.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-4, 9-12, 15, 16, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998) in view of Buechler et al. (U.S. Patent No. 5,795,725, Aug. 8, 1998), Baig (*American Heart Journal*, 1998, Vol. 135, ppS216-S230), Kline et al. (*Annals of Emergency Medicine*, February 2000, Vol. 35, pp168-180), and Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577).

Jackowski teaches that the emergency room physician is faced with a dilemma when a patient presents with chest pain and the cause of the chest pain must be determined as soon as possible so that the optimum method of treatment can be

selected (see entire document, particularly column 1, lines 34-38). Specifically, the physician must know if the pain is cardiac in origin or if it originates from some other source as chest pain can result from many causes: gastric discomfort (e.g., indigestion), pulmonary distress, pulmonary embolism, dyspnea, musculoskeletal pain (pulled muscles, bruises) indigestion, pneumothorax, cardiac non-coronary conditions, and acute ischemic coronary syndromes (AICS, column 1, lines 38-50). Diagnosis of the cause of chest pain requires differentiation between these conditions, which is difficult because of the similarity of the symptoms (column 2, lines 49-51). Nevertheless, an accurate diagnosis is critical to the health of a patient suffering from chest pain, particularly if the cause is MI (column 2, lines 51-53). It has been known for many years that during a cardiac event, heart tissue releases certain molecules, typically protein molecules, which are characteristic of the event and certain of them are released as a result of both UA and MI, others are released as a result of MI (column 1, lines 53-57). It would appear that the physician could recognize UA and MI simply by selecting cardiac markers or analytes with appropriate ischemic specificity and diagnostic sensitivity and identifying them with antibodies having the required antigen/antibody reactivity (column 2, line 65-column 3, line 2). Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for detection of MI among patients suffering from chest pain in order to distinguish one cardiovascular disorder from another (column 8, lines 48-54 and column 10, lines 21-51). However, Jackowski fails to teach a method, wherein B-type natriuretic peptide (BNP) and free and complexed troponin T are used as a plurality of

subject-derived markers to characterize a subject's risk of having developed or of developing a pulmonary embolism based on the amount of BNP, free and complexed troponin T, and D-dimer and wherein the amount of at least one of the subject-derived markers is not compared to a predetermined threshold amount.

Buechler et al. teaches assays and methods for the detection and quantification of cardiac specific troponin I and troponin T in body fluids as an indicator of MI (see entire document, particularly Abstract). An understanding of the conformational changes of troponin I and troponin T and the heterogeneity of the proteins in the blood is critical for the development of accurate diagnostic procedures for measuring troponin I and troponin T concentrations (column 2, lines 29-43). Buechler et al. teaches antibodies that specifically recognize troponin I and T in the following forms: 1) intramolecularly oxidized and reduced cysteines, 2 (binary complexes of troponin I and T, of troponin I and C, of troponin T and C and 3) ternary complex of troponin I, T and C (column 3, lines 16-41). The clinical impact of an immunoassay measuring only the free troponin I or T from a patient experiencing MI can be very significant (column 5, lines 59-61). Since the binding of troponin I and T to troponin components in the blood will be variable, depending on the troponin component concentrations, an analysis of the bound and free from of the troponin I and T in the blood must be considered (column 5, lines 61-65).

Baig et al. teaches that plasma brain-type natriuretic peptide (BNP) has a prognostic significance after MI (see entire document, particularly pS224, left column 2nd paragraph). The elevation of plasma BNP is generally longer lived than that of ANP

after MI and has in one study been shown to exhibit a secondary rise at day 5 after MI (pS224, left column 2nd paragraph).

Kline et al. teaches that D-dimer assay offers many of the characteristics that might define the ideal screening tool for pulmonary embolism (see entire document, particularly). The tests are safe, noninvasive, rapid, and inexpensive when compared with the cost of diagnostic imaging. Combined with an objective test of pulmonary gas exchange, D-dimer assays have sufficient sensitivity to reliably distinguish embolism diagnosis (p169, left column, Introduction, 3rd paragraph and p177, right column, Implications for Research, 1st paragraph).

Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests (see entire document, particularly Abstract). The use of ROC plots has many advantages (p568, left column, *Advantages of ROC Plots*). It is a comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test. It does not require selection of a particular decision threshold because the whole spectrum of possible decision thresholds is included. It is independent of prevalence: No care need be taken to obtain samples with representative prevalence. It provides a direct visual comparison between tests on a common scale, whereas both dot diagrams and frequency histograms require different plots if the scales differ. It requires no grouping or binning of data, as do frequency histograms. Its specificity and sensitivity are readily accessible, in contrast to dot diagrams and frequency histograms.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ a method of detecting free and complexed cardiac troponin T as taught by Buechler et al. and a method of detecting BNP as taught by Baig et al. in the method of Jackowski in order to distinguish MI amongst patients suffering from common symptom of chest pain, which includes patients suffering from pulmonary embolism. The advantage of using two biomarkers free and complexed cardiac troponin T and BNP, which have been shown be associated with MI, in addition to the three biomarkers (creatine-kinase-MB, myoglobin, and total cardiac troponin I) of Jackowski provides the motivation to combine the teachings of Jackowski, Buechler et al., and Baig et al. with a reasonable expectation of success as the use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain, which includes patients suffering from pulmonary embolism. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980). In addition, it would have been obvious to one of ordinary skill in the art at the time of the invention to include a method of distinguishing pulmonary embolism on the basis of D-dimer assays combined with an objective test of pulmonary gas exchange as taught by Kline et al. in the method of Jackowski in view of Buechler et al. Baig, and Zweig et al. in order to accurately distinguish pulmonary embolism amongst patients suffering from common symptom of chest pain. The advantage of using a screening assay for pulmonary embolism, which is safe, noninvasive, rapid, and inexpensive, provides the motivation to

combine the teachings of Jackowski and Kline et al. with a reasonable expectation of success. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use ROC evaluation method of Zweig et al., in which a particular (predetermined) threshold amount is not required, in the method of Jackowski in order to accurately and specifically determine clinical evaluation of laboratory tests of Jackowski. The advantage of analyzing laboratory test results with comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test, direct visual comparison between tests on a common scale, no grouping or binning of data, and readily accessible specificity and sensitivity provides the motivation to combine the teachings of Jackowski and Zweig et al. with a reasonable expectation of success.

16. Claims 5-8, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998) in view of Buechler et al. (U.S. Patent No. 5,795,725, Aug. 8, 1998), Baig (*American Heart Journal*, 1998, Vol. 135, ppS216-S230), Kline et al. (*Annals of Emergency Medicine*, February 2000, Vol. 35, pp168-180), and Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Holvoet et al. (U.S. Patent No. 6,309,888, Filed Sept. 4, 1998).

Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. teaches a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above.

However, Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. fails to teach a method, further comprising assaying the sample for the presence or amount of C-reactive protein.

Holvoet et al. teaches a method of detecting plurality of markers for accurate diagnosis of MI (see entire document, particularly column 21, lines 52-65). The markers include OxLDL, MDA-modified LDL, troponin, and C-reactive protein (column 21, lines 52-65). The area under the ROC-curve (AUC) measures diagnostic accuracy of a marker, where minimum value of 0.5 is required for a diagnostic marker (column 21, lines 52-65). The markers including OxLDL, MDA-modified LDL, troponin, and C-reactive protein (CRP) have an AUC above the minimum AUC value of 0.5 (column 21, lines 52-65).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include additional markers of MI including CRP as taught by Holvoet et al. in the method of Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. in order to accurately diagnose MI amongst patients suffering from common symptom of chest pain. The advantage of accurately diagnose MI amongst patients suffering from common symptom of chest pain provides the motivation to combine teachings of Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. and Holvoet et al. with a reasonable expectation of success as use of multiple markers would provide more accurate diagnostic methods for MI. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the

prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

17. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998) in view of Buechler et al. (U.S. Patent No. 5,795,725, Aug. 8, 1998), Baig (*American Heart Journal*, 1998, Vol. 135, ppS216-S230), Kline et al. (*Annals of Emergency Medicine*, February 2000, Vol. 35, pp168-180), and Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Heeschan et al. (The Lancet, 1999, Vol. 354, pp1757-1762).

Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. teaches a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. fails to teach a method, wherein the correlating step comprises comparing at least one marker amount to a predetermined threshold level.

Heeschen et al. teaches a method of measuring cardiac troponin T (free and complexed) concentration in patients for diagnostic and risk stratification of patients with acute coronary syndromes such as MI (see entire document, particularly Abstract). Patients with positive troponin T (greater than a threshold concentration of 0.1 μg/L) received tirofiban infusion therapy to effectively lower the incidence of death and MI (p1760, left column, *Troponin T*, 3rd paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating free and complexed cardiac troponin T levels in patients to a predetermined threshold level as taught by Heeschen et al. in the method of Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. in order to assess diagnostic and risk stratification of patients with acute coronary syndromes such as MI. The advantage of selecting a treatment option associated with a threshold level of free and complexed troponin T levels in patients provides the motivation to combine the teachings of Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al. and Heeschen et al. with a reasonable expectation of success.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Application No. 10/330,696

A. Claims 1-3, 9-12, 15, and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 10/330,696 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577).

The copending Application recites a method for analyzing a subject sample for a plurality of subject-derived markers selected to distinguish MI, pulmonary embolism, and congestive hear failure comprising assaying the sample for the presence or amount of BNP, free and complexed cardiac troponin T, and D-dimer to characterize the subject's risk of having developed or of developing MI, pulmonary embolism, and congestive hear failure. However, the copending Application fails to recite a method, wherein the amount of at least one or more subject-derived markers are not compared to a predetermined threshold amount.

Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use ROC evaluation method of Zweig et al., in which a particular (predetermined) threshold amount is not required, in the method of

the copending Application in order to accurately and specifically determine clinical evaluation of laboratory tests of the copending Application. The advantage of analyzing laboratory test results with comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test, direct visual comparison between tests on a common scale, no grouping or binning of data, and readily accessible specificity and sensitivity provides the motivation to combine the claims of the copending Application and the teachings Zweig et al. with a reasonable expectation of success.

B. Claims 4 and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 10/330,696 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claims 1, 3, 9, and 11 above, and further in view of Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, further comprising a step of assaying the sample for the presence or amount of myoglobin.

Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for

detection of MI among patients suffering from chest pain (column 10, lines 21-51) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of detecting additional markers of MI such as creatine-kinase-MB, myoglobin, and total cardiac troponin I as taught by Jackowski in the method of the copending Application in view of Zweig et al. in order to distinguish MI amongst patients suffering from common symptom of chest pain. The advantage of using additional biomarkers such as creatine-kinase-MB, myoglobin, and total cardiac troponin I, which have been shown be associated with MI, in addition to the biomarkers of the copending Application provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Jackowski with a reasonable expectation of success as use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

C. Claims 5-7 and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 10/330,696 in view of Zweig et al. (*Clinical Chemistry*,

1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Holvoet et al. (U.S. Patent No. 6,309,888, Filed Sept. 4, 1998).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, further comprising assaying the sample for the presence or amount of C-reactive protein.

Holvoet et al. teaches a method of detecting plurality of markers including OxLDL, MDA-modified LDL, troponin, and C-reactive protein for accurate diagnosis of MI as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include additional markers of MI including CRP as taught by Holvoet et al. in the method of the copending Application in view of Zweig et al. in order to accurately diagnose MI amongst patients suffering from common symptom of chest pain. The advantage of accurately diagnose MI amongst patients suffering from common symptom of chest pain provides the motivation to combine claims of the copending Application in view of Zweig et al. and the teachings of Holvoet et al. with a reasonable expectation of success as use of multiple markers would provide more accurate diagnostic methods for MI. Further, it has long been held that it is obvious to combine two compositions

each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

D. Claims 8 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 10/330,696 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) and Holvoet et al. (U.S. Patent No. 6,309,888, Filed Sept. 4, 1998) as applied to claims 5, 7, and 13 above, and further in view of Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998).

The copending Application in view of Zweig et al. and Holvoet et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. and Holvoet et al. fails to recite a method, further comprising a step of assaying the sample for the presence or amount of myoglobin.

Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for detection of MI among patients suffering from chest pain (column 10, lines 21-51) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of detecting additional markers of MI such as creatine-kinase-MB, myoglobin, and total cardiac troponin

I as taught by Jackowski in the method of copending Application in view of Zweig et al. and Holvoet et al. in order to distinguish MI amongst patients suffering from common symptom of chest pain. The advantage of using additional biomarkers such as creatine-kinase-MB, myoglobin, and total cardiac troponin I, which have been shown be associated with MI, in addition to the biomarkers of the copending Application provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Holvoet et al. and Jackowski with a reasonable expectation of success as use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

E. Claim 17 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 10/330,696 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Heeschan et al. (The Lancet, 1999, Vol. 354, pp1757-1762).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above.

However, the copending Application in view of Zweig et al. fails to recite a method, wherein the correlating step comprises comparing at least one marker amount to a predetermined threshold level.

Heeschen et al. teaches a method of measuring cardiac troponin T (free and complexed) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating free and complexed troponin T levels in patients to a predetermined threshold level as taught by Heeschen et al. in the method of the copending Application in view of Zweig et al. in order to assess diagnostic and risk stratification of patients with acute coronary syndromes such as MI. The advantage of selecting a treatment option associated with a threshold level of free and complexed troponin T levels in patients provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Heeschen et al. with a reasonable expectation of success.

This is a provisional obviousness-type double patenting rejection.

20. Application No. 10/728,067

A. Claims 1-3, 5-7, 9-11, 13, 15, and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending Application No. 10/728,067 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577).

The copending Application recites a method for analyzing a subject sample for a plurality of subject-derived markers selected to distinguish MI, pulmonary embolism, congestive hear failure, and other cardiovascular disorders comprising assaying the sample for the presence or amount of BNP, free and complexed cardiac troponin T, CRP, and D-dimer to characterize the subject's risk of having developed or of developing MI, pulmonary embolism, congestive hear failure, and other cardiovascular disorders. However, the copending Application fails to recite a method, wherein the amount of at least one or more subject-derived markers are not compared to a predetermined threshold amount.

Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use ROC evaluation method of Zweig et al., in which a particular (predetermined) threshold amount is not required, in the method of the copending Application in order to accurately and specifically determine clinical evaluation of laboratory tests of the copending Application. The advantage of analyzing laboratory test results with comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test, direct visual comparison between tests on a common scale, no grouping or binning of data, and readily accessible specificity and sensitivity provides the motivation to combine the claims of the copending Application and the teachings of Zweig et al. with a reasonable expectation of success.

B. Claims 4, 8, 12, and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending Application No. 10/728,067 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claims 1, 3, 5, 7, 9, 11, and13 above, and further in view of Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, further comprising a step of assaying the sample for the presence or amount of myoglobin.

Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for detection of MI among patients suffering from chest pain (column 10, lines 21-51) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of detecting additional markers of MI such as creatine-kinase-MB, myoglobin, and total cardiac troponin I as taught by Jackowski in the method of the copending Application in view of Zweig et al. in order to distinguish MI amongst patients suffering from common

symptom of chest pain. The advantage of using additional biomarkers such as creatine-kinase-MB, myoglobin, and total cardiac troponin I, which have been shown be associated with MI, in addition to the biomarkers of the copending Application provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Jackowski with a reasonable expectation of success as use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

C. Claim 17 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending Application No. 10/728,067 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Heeschan et al. (The Lancet, 1999, Vol. 354, pp1757-1762).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a

method, wherein the correlating step comprises comparing at least one marker amount to a predetermined threshold level.

Heeschen et al. teaches a method of measuring cardiac troponin T (free and complexed) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating free and complexed troponin T levels in patients to a predetermined threshold level as taught by Heeschen et al. in the method of the copending Application in view of Zweig et al. in order to assess diagnostic and risk stratification of patients with acute coronary syndromes such as MI. The advantage of selecting a treatment option associated with a threshold level of free and complexed troponin T levels in patients provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Heeschen et al. with a reasonable expectation of success.

This is a provisional obviousness-type double patenting rejection.

21. Application No. 11/205,571

A. Claims 1-3, 5-8, and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 11/205,571 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577).

The copending Application recites a method for analyzing a subject sample for a plurality of subject-derived markers selected to distinguish MI, comprising assaying the sample for the presence or amount of BNP, free and complexed cardiac troponin T, and CRP to characterize the subject's risk of having developed or of developing MI. However, the copending Application fails to recite a method, wherein the amount of at least one or more subject-derived markers are not compared to a predetermined threshold amount.

Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use ROC evaluation method of Zweig et al., in which a particular (predetermined) threshold amount is not required, in the method of the copending Application in order to accurately and specifically determine clinical evaluation of laboratory tests of the copending Application. The advantage of analyzing laboratory test results with comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test, direct visual comparison between tests on a common scale, no grouping or binning of data, and readily accessible specificity and sensitivity provides the motivation to combine the claims of the copending Application and the teachings of Zweig et al. with a reasonable expectation of success.

B. Claims 4 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 11/205,571 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claims 1, 3, and 5 above, and further in view of Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, further comprising a step of assaying the sample for the presence or amount of myoglobin.

Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for detection of MI among patients suffering from chest pain (column 10, lines 21-51) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of detecting additional markers of MI such as creatine-kinase-MB, myoglobin, and total cardiac troponin I as taught by Jackowski in the method of the copending Application in view of Zweig et al. in order to distinguish MI amongst patients suffering from common symptom of chest pain. The advantage of using additional biomarkers such as creatine-kinase-MB, myoglobin, and total cardiac troponin I, which have been

shown be associated with MI, in addition to the biomarkers of the copending Application provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Jackowski with a reasonable expectation of success as use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

C. Claim 17 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 11/205,571 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Heeschan et al. (The Lancet, 1999, Vol. 354, pp1757-1762).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, wherein the correlating step comprises comparing at least one marker amount to a predetermined threshold level.

Heeschen et al. teaches a method of measuring cardiac troponin T (free and complexed) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating free and complexed troponin T levels in patients to a predetermined threshold level as taught by Heeschen et al. in the method of the copending Application in view of Zweig et al. in order to assess diagnostic and risk stratification of patients with acute coronary syndromes such as MI. The advantage of selecting a treatment option associated with a threshold level of free and complexed troponin T levels in patients provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Heeschen et al. with a reasonable expectation of success.

This is a provisional obviousness-type double patenting rejection.

22. Application No. 11/450,150

A. Claims 1-3, 5-7, 9-11, 13, 15, and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 11/450,150 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577).

The copending Application recites a method for analyzing a subject sample for a plurality of subject-derived markers selected to distinguish pulmonary embolism comprising assaying the sample for the presence or

amount of BNP, free and complexed cardiac troponin T, CRP, and D-dimer to characterize the subject's risk of having developed or of developing pulmonary embolism. However, the copending Application fails to recite a method, wherein the amount of at least one or more subject-derived markers are not compared to a predetermined threshold amount.

Zweig et al. teaches receiver-operating characteristics (ROC) plots as an evaluation tool in clinical performance of laboratory tests as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use ROC evaluation method of Zweig et al., in which a particular (predetermined) threshold amount is not required, in the method of the copending Application in order to accurately and specifically determine clinical evaluation of laboratory tests of the copending Application. The advantage of analyzing laboratory test results with comprehensive representation of pure accuracy, i.e. discriminating ability, over the entire range of the test, direct visual comparison between tests on a common scale, no grouping or binning of data, and readily accessible specificity and sensitivity provides the motivation to combine the claims of the copending Application and the teachings of Zweig et al. with a reasonable expectation of success.

B. Claims 4, 8, 12, and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 11/450,150 in view of Zweig et al.

(*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claims 1, 3, 5, 7, 9, 11, and13 above, and further in view of Jackowski (U.S. Patent No. 5,710,008, Jan. 20, 1998).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, further comprising a step of assaying the sample for the presence or amount of myoglobin.

Jackowski teaches a method of detecting multiple markers associated with MI including creatine-kinase-MB, myoglobin, and total cardiac troponin I for detection of MI among patients suffering from chest pain (column 10, lines 21-51) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of detecting additional markers of MI such as creatine-kinase-MB, myoglobin, and total cardiac troponin I as taught by Jackowski in the method of the copending Application in view of Zweig et al. in order to distinguish MI amongst patients suffering from common symptom of chest pain. The advantage of using additional biomarkers such as creatine-kinase-MB, myoglobin, and total cardiac troponin I, which have been shown be associated with MI, in addition to the biomarkers of the copending Application provides the motivation to combine the claims of the copending

Application in view of Zweig et al. and the teachings of Jackowski with a reasonable expectation of success as use of additional biomarkers would provide more accurate method of distinguishing MI amongst patients suffering from common symptom of chest pain. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerhoven*, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

C. Claim 17 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-63 of copending Application No. 11/450,150 in view of Zweig et al. (*Clinical Chemistry*, 1993, Vol. 39, pp567-577) as applied to claim 1 above, and further in view of Heeschan et al. (The Lancet, 1999, Vol. 354, pp1757-1762).

The copending Application in view of Zweig et al. recites a method of analyzing a subject sample for a plurality of subject markers selected to distinguish amongst a plurality of cardiovascular disorders as discussed above. However, the copending Application in view of Zweig et al. fails to recite a method, wherein the correlating step comprises comparing at least one marker amount to a predetermined threshold level.

Heeschen et al. teaches a method of measuring cardiac troponin T (free and complexed) as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating free and complexed troponin T levels in patients to a predetermined threshold level as taught by Heeschen et al. in the method of the copending Application in view of Zweig et al. in order to assess diagnostic and risk stratification of patients with acute coronary syndromes such as MI. The advantage of selecting a treatment option associated with a threshold level of free and complexed troponin T levels in patients provides the motivation to combine the claims of the copending Application in view of Zweig et al. and the teachings of Heeschen et al. with a reasonable expectation of success.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

23. Written description rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. 112, first paragraph

Applicants' arguments filed on January 11, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejections.

Applicant's argument regarding "subject-derived markers" (p8-12) has been fully considered, but they are not persuasive in view of previously stated grounds of rejections. As stated previously, instant claims recite a genus "subject-derived markers" related to blood pressure regulation, myocardial injury, inflammation, and coagulation and hemostasis as part of the invention without providing a physical structure or

testable functional activity for the "subject-derived markers." Since presumably not all of the markers would be indicative of all cardiovascular disorders, the specification provides data for fewer than 9 different marker combinations for distinguishing a plurality of cardiovascular disorders, which only include myocardial infarction (MI), congestive heart failure (CHF), acute coronary syndrome, unstable angina, and pulmonary embolism, and the genus of "subject-derived markers" are very large as set forth in the previous written description rejection, the genus of "subject-derived markers" lack a common structure essential for their function (see the description of the markers in the specification as set forth in item #), and the claims do not require any particular structure basis or testable functions be shared by the instant "subject-derived markers."

The claims are directed to using a plurality of combinations of subject-derived markers. While the specification only outlines nine combinations of subject-derived markers (Examples and pp30-31 of the specification) for characterizing a subject's risk of having developed or developing a cardiovascular disorder, the specification does not provide other combinations involving subject-derived markers recited in the present claims.

According to MPEP § 2163, a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient

to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

The present claims recites plurality of combinations of subject-derived markers selected to characterize a subject's risk of having developed or developing a cardiovascular disorder as set forth above, but the specification only discloses nine combinations of subject-derived markers among the possible combinations of markers selected at least one of each from 8 markers selected to identify MI (as discussed above), 2 markers selected to identify CHF (as discussed above), 12 markers selected to identify pulmonary embolism (as discussed above), and other subject-derived markers. Further, there is unpredictability in the results obtained from species other

than those specifically enumerated, as not all the subject-derived markers as currently recited can be used to characterize a subject's risk of having developed or developing a cardiovascular disorder as disclosed in the specification. Therefore, the specification fails to provide written description for the genus of combinations of subject-derived markers selected to identify the presence or absence or MI, CHF, and pulmonary embolism for identifying the presence or absence of MI, CHF, or pulmonary embolism as currently recited in the claims.

Taken together, instant claims do not satisfy the written description requirement under 35 U.S.C. 112, first paragraph.

24. Enablement rejection of claims 1-10, 13, and 15-17 under 35 U.S.C. 112, first paragraph

Applicants' arguments filed on February 29, 2008 have been fully considered but they are not persuasive in view of previously stated grounds of rejections.

State of the prior art

Applicant's argument regarding the state of the prior art has been fully considered, but is not found persuasive in view of previously stated grounds of rejection. The use of biomarkers and the subject-derived markers recited in disclosed in the specification are indeed well known in the art. Applicant's assertion that biomarkers are routinely used in the art for diagnosis and prognosis of individual cardiac conditions including the three recited conditions, MI, CHF, and pulmonary embolism overly simplifies the process of using biomarkers for diagnostic/prognostic indicators.

Although applicant cites several references (Kemp et al., Felker et al., and Biasucci) for teachings of use of biomarkers in diagnostic assays, it is clear from applicant's own disclosure that many of the subject-derived markers recited in claims are present in plurality of cardiovascular disorders or not associated with cardiovascular disorders.

According to the specification, the subject-derived markers and their association with various cardiovascular and other disease conditions have been discussed above (see item 10).

Since the markers disclose in the specification lack specificity required to detect/characterize a subject's risk of developing a cardiovascular disorder, the specification only outlines art-recognized methodology that can be used in conducting investigational studies to test and validate biomarkers for various diagnostic purposes. Such a general roadmap amounts to an invitation to conduct further research, rather than a specific direction required to enable one of ordinary skill in the art to understand and carry out the invention. Hence, this general outline for how to test and validate different sets of biomarkers for characterizing the risk of having developed or developing cardiovascular disorders fails to constitute an enabling disclosure in light of complexity, unpredictability and laborious nature of biomarker validation (discussed further below) and furthermore fails to provide one skilled in the art with any reasonable expectation of success in using any particular combination of markers to identify the presence or absence of a plurality of conditions comprising MI, CHF, and

pulmonary embolism. The specification sets forth a research plan, not an invention to be practiced. Therefore, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed "subject-derived markers" to characterize the risk of having developed or developing cardiovascular disorders.

Further, applicant's argument that the Examiner seeks to paint the state of the prior art concerning the use of biomarkers generally in a negative light has been fully considered but is not found persuasive essentially for the reasons of record. As stated in the previous Office Action dated October 31, 2007 (item 9), Bast, Jr. et al. (Clinical Cancer Research, 2005, Vol. 11, pp6103-6108) points to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p6105, right column). Similarly, LaBaer et al. (Journal of Proteome Research, 2005, Vol. 4, pp1053-1059) teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p1053, paragraph bridging the left and right columns). In addition, Baker (Nature Biotechnology, 2005, Vol. 23, pp297-304) speaks to the unpredictability involved in clinically applying biomarkers (p298, Walking on Thin Ice). As a result, in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid

biomarkers of the particular cardiovascular disorder, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods. This type of clinical investigations would need to be done for each type of cardiovascular disorder. In addition, one skilled in the art would also need to determine what levels or ranges of levels of each of the markers would be indicative of each type of cardiovascular disorder. Such investigative research to test and validate all of the biomarkers for use in distinguishing a cardiovascular disorder is not of a routine nature and clearly represents an undue burden.

The relative level of skill in the art

Applicant's contention that the skill in the art is high as the skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients has been fully considered but is not found persuasive essentially for the reasons of record and the response of arguments set forth above. Although, the specification outlines extensive list of potential biomarkers involved in plurality of cardiovascular disorders, one skilled in the art would not be able to make and use the claimed "subject-derived markers" to characterize the risk of having developed or developing cardiovascular disorders since one skilled in the art would first need to determine whether any given set of markers

claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid biomarkers of cardiovascular disorders, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods based on the current state of the art as discussed above.

The quantity of experimentation necessary

Applicant's assertion that little is required in combining known biomarkers to characterize the risk of having developed or developing cardiovascular disorders since the specification describes in substantial detail a large number or exemplary markers has been fully considered but is not found persuasive essentially for the reasons of record and the response of arguments set forth above.

The claims are directed to using a plurality of combinations of subject-derived markers. While the specification only outlines six combinations of subject-derived markers comprising BNP related peptides, D-dimer, and cardiac troponin (pp30-31 and pp103-p110) for diagnoses of MI, CHF, and pulmonary embolism, the specification does not provide other combinations involving subject-derived markers recited in the present claims.

In *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the court found that several claims were not supported by an enabling disclosure "[t]aking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of the particular cyanobacterial genera operative in the claimed invention...." The claims at issue were not limited to any particular genus or species of cyanobacteria and the specification mentioned nine genera and the working examples employed one species of cyano-bacteria.

The present claims recites plurality of combinations of subject-derived markers selected to characterize the risk of having developed or developing cardiovascular disorders as set forth above, but the specification only discloses nine combinations of subject-derived markers (Examples and pp30-31 of the specification) among the possible combinations of markers selected at least one of each from 8 markers selected to identify MI (as discussed above), 2 markers selected to identify CHF (as discussed above), 12 markers selected to identify pulmonary embolism (as discussed above), and other markers of plurality of cardiovascular disorders disclosed throughout the specification as set forth above. Therefore, the specification fails to teach the skilled artisans genus of combinations of subject-derived markers selected to characterize the risk of having developed or developing cardiovascular disorders as currently recited in the claims since the specification only discloses only six combinations of subject-derived markers for characterize the risk of having developed or developing

cardiovascular disorders among large number of possible combinations of markers.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108, F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 (1996) (stating, in context of the utility requirement, that a "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id.

Applicant's argument that no scientific evidence or reasoned scientific explanation as to why the markers described in the specification could not each be used in the claimed invention as taught in the specification has been fully considered, but is not found persuasive essentially for the reasons of record and arguments addressed in the state of the prior art section, which includes reasons as to why some of the subject-derived markers described in the specification could not each be used in the claimed invention based on the descriptions of the markers in the specification.

The predictability of the art

Applicant's argument regarding the predictability of the art has been fully considered but is not found persuasive essentially for the reasons of record and arguments addressed above and herein.

Applicant's contention that the opinions of the broad allegations of speculative disclosure and difficulties that may be encountered in practice are legally insufficient for rejection a claim under enablement requirement has been fully considered, but is not found persuasive essentially for the reasons of record. As set forth above in the state of the prior art section, not all the individual subject-derived markers can be used to characterize the risk of having developed or developing cardiovascular disorders, which is supported by the descriptions of the markers in the specification. Further, Bast, Jr. et al. point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p6105, right column). Similarly, LaBaer et al. teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p1053, paragraph bridging the left and right columns). In addition, Baker speaks to the unpredictability involved in clinically applying biomarkers (p298, Walking on Thin Ice). As a result, in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid biomarkers to characterize the risk of having developed or developing cardiovascular disorders, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether

statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods based on the current state of the art. In addition, one skilled in the art would also need to determine what levels or ranges of levels of each of the markers would be indicative of each type of cardiovascular disorder. Such investigative research to test and validate all of the biomarkers for use in distinguishing a cardiovascular disorder is not of a routine nature and clearly represents an undue burden. As correctly stated by the appellant, the test of enablement is whether or not one skilled in the art could reasonably make or use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation. Therefore, the specification does not enable one skilled in the art to reasonably make or use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation.

The amount of direction or guidance

Applicant's arguments regarding the amount of direction or guidance has been fully considered but are not persuasive essentially for the reasons of record and arguments set forth above in the quantity of experimentation necessary section.

The breadth of the claims

Applicant's arguments regarding the amount of direction or guidance has been fully considered but are not persuasive essentially for the reasons of record and arguments set forth above in the quantity of experimentation necessary section.

Taken together, the one skilled in the art would not be able to perform the claimed methods using the specification and the knowledge available in the art without undue experimentation as the rejection does consider the knowledge available in the art and is based on unpredictability associated with validation of biomarkers for clinical use.

25. Rejection of claims 1-4, 9-12, 15, 16, 37, and 38 under 35 U.S.C. 103(a) as being unpatentable over Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al.

Applicant's arguments filed on February 29, 2008 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed herein.

Applicant's argument that Zweig et al. does not contemplate the claimed limitation of using marker value in patient management without comparing to a predetermined threshold is not found persuasive. While Zweig et al. does teach methods of comparing to a predetermined threshold, Zweig et al. further teaches other methods ("global approach"), which do not rely on the selection of a particular decision threshold (p570, left column, 2nd paragraph). Zweig et al. teaches that the global approach of comparing entire ROC plots does not involve comparing to a

predetermined threshold (pp569-570, *Statistical Comparison of Multiple Tests by Use of ROC Plots*).

Applicant's argument that Zweig et al. teaches that the use of the test for patient management, which requires a decision threshold selection stated in the declaration by Dr. Anderberg dated January 11, 2007 has been fully considered but is not found persuasive essentially for the reasons of record. Although Zweig et al. does a method using a decision threshold for assessment of patient management, Zweign et al. further teaches a number of different analyses using ROC curves, one of which being the global approach of comparing entire ROC plots, which does not involve comparing to a predetermined threshold as discussed above. In contrast to applicant's assertion that Zweig et al. does not teach the use of the global approach in diagnostic test for individual patient management, Zweig et al. does teach that the global approach of comparing entire ROC plots can be used within the same patient for diagnostic evaulation of a cardiovascular disease (CAD, p570, left column, 3rd paragraph).

Since the combination of references in the rejection of claims 1-4, 9-12, 15, 16, 37, and 38 does teach or suggest each and every limitation of the claims and does not teach away from the claimed methods, the rejection of claims 1-4, 9-12, 15, 16, 37, and 38 under 35 U.S.C. 103(a) has been maintained.

26. Rejection of claims 5-8, 13, and 14 under 35 U.S.C. 103(a) as being unpatentable over Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al., and further in view of Holvoet et al.

Applicant's arguments filed on February 29, 2008 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed in item 25 above.

In view of foregoing response to arguments, the rejection of claims 5-8, 13, and 14 under 35 U.S.C. 103(a) has been maintained.

27. Rejection of claim 17 under 35 U.S.C. 103(a) as being unpatentable over Jackowski in view of Buechler et al., Baig, Kline et al., and Zweig et al., and further in view of Heeschan et al.

Applicant's arguments filed on February 29, 2008 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed in item 25 above.

In view of foregoing response to arguments, the rejection of claim 17 under 35 U.S.C. 103(a) has been maintained.

28. Double Patenting Rejections

Applicant's arguments filed on February 29, 2008 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed in item 25 above and herein.

Applicant's argument that the double patenting rejections set forth in items 26-29 of the previous Office Action dated September 11, 2006 are improperly found on the "teachings" of various copending patent applications is not found persuasive. All the double patenting rejections as a whole are rejected over the claims of the copending

applications as clearly indicated in the first rejection headings of each rejection. For example, claims 58-71 of copending Application No. 10/330,696 recite a method for analyzing a subject sample for a plurality of subject-derived markers selected to distinguish MI, pulmonary embolism, and congestive hear failure (as recited in claim 58) comprising assaying the sample for the presence or amount of BNP, free and complexed cardiac troponin T, and D-dimer (as recited in claim 60) to characterize the subject's risk of having developed or of developing MI, pulmonary embolism, and congestive hear failure. Therefore, the obvious-type double patenting rejections have been made based only on claims. Further, the obvious-type double patenting rejections have been modified to reflect the issues of claims rather than the "teachings" of the copending Applications.

In view of foregoing response to arguments, all the provisional rejections on the ground of nonstatutory obviousness-type double patenting have been maintained.

Conclusion

29. No claim is allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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